



October 26, 2015

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

Subject: Comments of USP on Nonproprietary Naming of Biological Products  
Draft Guidance for Industry, Docket No. FDA-2013-D-1543

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Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) "Nonproprietary Naming of Biological Products" Draft Guidance for Industry" (Draft Guidance). The Draft Guidance describes FDA's proposal that all biological products bear a nonproprietary name that includes a product-specific FDA-designated suffix. Along with the Draft Guidance, FDA issued a Proposed Rule, "Designation of Official Names and Proper Names for Certain Biological Products," that sets forth proposed names for six products based on the naming convention proposed in the Draft Guidance. USP will be commenting separately on the Proposed Rule.

USP shares FDA's goal of improving patient safety across all medicines. Throughout our nearly 200-year history we have worked to ensure that patients receive high-quality, safe and effective medicines. USP achieves this through our legally recognized role in setting public standards for the identity, purity, quality, strength, packaging, and labeling of drugs and biologics. As part of this role, USP is involved in a well-established drug naming system, which includes naming of biologics. USP remains committed to fulfilling this role as we have since the beginning of drug approval and biologic licensing laws in the United States.

USP acknowledges FDA's efforts to advance the successful implementation of the Biologics Price Competition and Innovation Act (BPCIA). We understand that the naming approach for biologics in the Draft Guidance reflects FDA's interest in preventing inadvertent substitution of and facilitating pharmacovigilance for biological products. At the same time, USP believes it is critically important to maintain a uniform and scientifically based naming approach that does not create unintended risks for patients and practitioners.

USP has set forth below a comprehensive set of comments that highlight the following key concepts: (1) USP has a well-established approach for setting standards for biologics and biotechnology-derived products that includes drug substances and drug products; (2) there is a scientifically based existing nonproprietary naming system, in which USP is a participant, for drugs and biologics that has protected patients for over a century; (3) USP appreciates FDA's challenge of ensuring safe use and facilitating pharmacovigilance, however, the use of a

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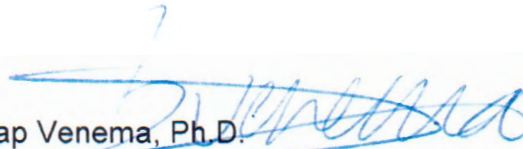
nonproprietary naming system to convey regulatory status could result in unintended consequences by employing the system in a way that was not intended; and (4) USP encourages FDA to consider alternative labeling solutions to the naming convention proposed in the Draft Guidance.

We appreciate FDA's efforts to address the challenges of implementing the biosimilars pathway, including naming, and acknowledge that these challenges are complex and often defy easy solutions. We stand ready to work collaboratively with FDA and stakeholders, using our current compendial process and legal recognition to help ensure that USP's quality standards continue to support and work in concert with the Agency's regulatory efforts to advance our common goal of protecting and promoting the public health. Our comments are further detailed below.

Thank you for your consideration of these comments.

If you have any questions, please feel free to contact Tina Morris, Senior Vice President, Science Global Biologics, at [tsm@usp.org](mailto:tsm@usp.org) or (301) 816-8347.

Sincerely,

  
Jaap Venema, Ph.D.  
Executive Vice President and Chief Science Officer



## I. USP'S LEGALLY RECOGNIZED ROLE IN ADVANCING PUBLIC HEALTH

USP is a scientific nonprofit organization that since 1820 has worked to advance public health through standards that help ensure the quality, safety, and benefit of medicines. USP develops its standards through Expert Committees consisting of leading scientific expert volunteers.

Public standards ensure product quality and consistency and are a critical part of the overall safety net that protects our medicines and the patients who use them. A public quality standard allows independent determination that a product has been made according to regulatory expectations for identity, strength, quality, and purity regardless of the manufacturer or manufacturing process.

The critical importance of a scientific public standard has long been recognized by patients, practitioners, regulatory agencies, and Congress. Starting in 1848, Congress turned to USP as a means of documenting the quality of a medicinal article in the Import Drugs Act. By the beginning of the 20<sup>th</sup> century, a specific role for USP standards was included in federal law—first in the adulteration provision of the 1906 Food and Drugs Act, and later in various provisions of the modern Federal Food, Drug, and Cosmetic Act (FDCA, 1938), most notably in both the adulteration and misbranding provisions. These provisions and others specify USP's role in creating nonproprietary names and related standards for identity, as well as standards for strength, quality, purity, packaging, and labeling.

USP's role in naming has clear statutory recognition under the FDCA. Under section 502(e), a drug is misbranded unless its label bears, to the exclusion of any other nonproprietary name, the established name. Section 502(e)(3) specifies that the "established name" of a drug or ingredient is: (A) The official name designated by FDA in accordance with section 508 of the FDCA; (B) The official title used for the drug or ingredient in an **official compendium such as USP or NF**, if FDA has not designated a name under (A); or (C) If no name has been established under (A) or (B), the common or usual name of the drug or ingredient. Under this provision, unless FDA has designated an "official name" under section 508, the "official title" used in the *United States Pharmacopeia and National Formulary (USP-NF)* becomes the established name. In order to designate an official name under section 508, FDA must go through a rulemaking process. FDA in practice and through its own regulation provides that FDA "will not routinely designate official names under section 508" of the FDCA.<sup>1</sup> If FDA does designate an established name under section 508, that name is to be used as the official name in the *USP-NF*.

Complementary to the naming provisions in Section 502 and 508, under FDCA 201(j) and 501(b) a drug "shall be deemed adulterated" if it purports to be, or is represented as, a drug

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<sup>1</sup> 21 CFR § 299.4(e). 21 CFR § 299.4(e) states, "The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common or usual name of the drug."

the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.

These provisions apply to biologics just as they do to all other drugs, whether such biologics are approved under the FDCA or licensed under the Public Health Service (PHS) Act. This is confirmed in the case of PHS Act biologics by PHS Act Section 351(j), which states that all PHS Act biological products are subject to the FDCA, other than the requirement of having an approved application under FDCA Section 505. Accordingly, a biological product that is licensed under the PHS Act nevertheless is subject to FDCA regulatory requirements, including notably the adulteration and misbranding provisions in Sections 501, 502 and 508.

The Biologics Price Competition and Innovation Act (BPCIA, 2009) creates an additional licensure pathway under the PHS Act for biological products that FDA determines to be biosimilar to or interchangeable with a reference product according to criteria specified in the statute. Like all other approved and licensed biologics, these biosimilar and interchangeable products must comply with the provisions described above: they must bear the established name as designated by USP or FDA, and must conform to compendial standards related to strength, quality or purity or risk being deemed adulterated and/or misbranded.

## **II. EXISTING WELL-ESTABLISHED NONPROPRIETARY NAMING SYSTEM FOR DRUGS AND BIOLOGICS**

Clear, consistent, and scientifically based names for drug substances and drug products are essential to helping practitioners, patients, and consumers use medications safely. Since USP began publishing the *United States Pharmacopeia* in 1820, our government and the public have relied on that compendium (now published together with the *National Formulary* as *USP–NF*) to provide nonproprietary names for medicines. USP's role in naming applies to both drug substances and drug products, and to all drugs, including biologics. USP has extensive experience in the naming of biologics, including naturally derived biologics (e.g., heparin), as well as recombinant protein therapeutics such as Filgrastim, Somatropin, Glucagon, and insulins. Despite the changes that have occurred over the years in the way these medicines are developed, manufactured, licensed, and/or administered, USP's role in naming has not changed; it is and has always been to provide scientifically based names that ultimately promote public health.

As medicines have evolved over the past nearly 200 years and the understanding of science has advanced, the time-tested approach of linking the official title in the *United States Pharmacopeia* (*USP*) on the label of a medicine to publicly available quality standards has created a single, consistent and reliable system proven to benefit public health. A USP monograph for a medicine helps ensure that what's on the label is actually in the bottle—that is, that the product is what it is purported to be, and in the right purity and strength. It does this by connecting the name of an article to a fixed standard of identity and quality (scientific criteria that uniquely identify the article).

USP's role in naming is part of a larger well-established naming system that has global significance. This system ensures the scientific consistency of nonproprietary names from the early drug development stage through the marketing of a drug or biologic. This system

involves the USP, FDA, and others working together to ensure a single naming convention, which to date has resulted in the establishment of well over 10,000 nonproprietary names for drugs and biologics.

This system starts early in the drug development stage (long before FDA approval or licensure of a medicine), when manufacturers seek an approved name for a drug substance. At an international level, the assignment of the International Nonproprietary Names (INN) is sponsored by the World Health Organization (WHO). In the United States, the United States Adopted Names (USAN) Council provides nonproprietary names for active ingredients. Founded in 1961, USAN is sponsored by the American Medical Association, the American Pharmacists Association, and USP, with active participation by FDA. Decisions reached by the USAN Council are unanimous and the results have been published by USP continually since 1963 in the *USP Dictionary of USAN and International Drug Names*.

Below is a USP-USAN Dictionary Entry that identifies all the names, codes, and identifiers that help link together all the relevant information on a given substance (Figure 1). This information includes a unique ingredient identifier (UNII) for each substance, generated by the joint FDA/USP Substance Registration System (SRS) which supports health information technology initiatives.

Figure 1.

	2	3	4	5	6
	Year published as USAN	Pronunciation guide	Official compendium in which title occurs	Molecular formula and weight	International nonproprietary name
U.S. Adopted Name <b>1</b>					<b>7</b> Chemical name(s)
Other nonproprietary name(s) <b>9</b>					<b>8</b> CAS registry number(s)
UNII code <b>15</b>					<b>10</b> Pharmacologic and/or therapeutic category
Brand name(s) <b>11</b>					<b>13</b> Code designation(s)
Manufacturer <b>12</b>					<b>14</b> Graphic formula

*Cephalexin [1967] (see a lex in) USP C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>6</sub>S H<sub>2</sub>O 365.41 [Cephalexin INN BAN and JAN] (1) 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo- monohydrate [6R-[6α, 7β-(R\*)]]- (2) (6R, 7R)-7-[(R)-2-Amino-2-phenylacetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate: (3) 7-(D-α-Amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate UNII: OBN7UD542Y CAS: 23325-78-2 CAS: 156807-1-2 [anhydrous] AnnBacteriol Keflet (Lilly), Keflex (Middlebrook) 066573*

In practice, this naming system is a very collaborative effort. USAN works closely with INN so that in most situations these names are aligned and a USAN name will be afforded INN status and vice versa. Neither USAN nor INN is recognized in federal law, and about 75% of the drug substances named by these organizations never actually make it to market.

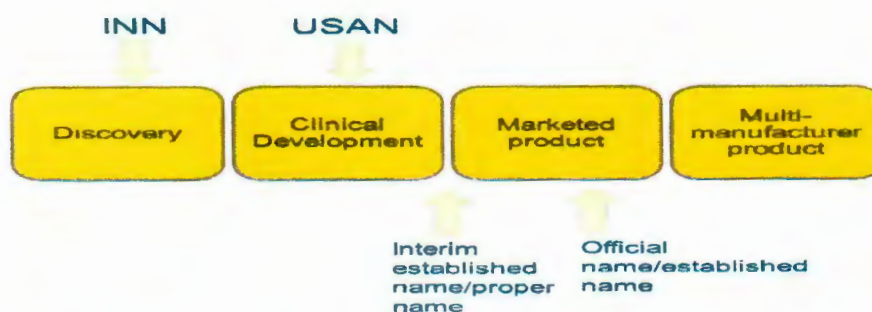
As USP develops a drug substance monograph for an approved product and creates an official title, it will generally align with the USAN nonproprietary name for the drug substance as USP is active in determining this name as part of USAN and shares an aligned scientific approach. USP will also establish a nonproprietary name for the drug product, as USAN names only drug substances. Like USAN and INN, USP, through its scientific expert

committees responsible for naming decisions, bases naming on the scientific attributes of the article which comprise its identity.<sup>2</sup>

When FDA approves a drug or licenses a biologic for marketing and there is already an applicable USP standard, the official title in the USP monograph is the designated nonproprietary name. When FDA approves a drug and there is no applicable USP standard—which is likely in the case of a New Drug Application (NDA) or Biologics License Application (BLA)—FDA assigns an interim established name that serves as the nonproprietary name (official established or proper name) until USP creates an applicable monograph.<sup>3</sup>

This link between INN, USAN and USP, and FDA's long-standing practice and policy to rely on the nonproprietary drug names established by USAN and USP, creates a clear and well-understood progression of naming activities throughout the drug lifecycle (Figure 2).

Figure 2.



Together these activities create a comprehensive, uniform system that works in concert with the naming provisions of the FDCA in the US, and in most cases results in global consistency across names.

<sup>2</sup> The USP Nomenclature, Safety and Labeling (NSL) Expert Committee is the decision-making body that designates official titles for the *USP-NF*. The committee does so in close consultation with the relevant expert committees that review and approve the associated monograph tests and specifications. The NSL Expert Committee in the review process carefully considers and works to align with existing INN and USAN names. FDA Government Liaisons actively participate in the NSL Expert Committee.

<sup>3</sup> Recent case law confirmed that FDA's long standing practice of assigning a name upon drug approval results only in an "interim" established name until an established name is provided in *USP-NF*. *Novartis v. Leavitt*, 435 F.3d 344 (D.C.Cir. 2006).

### III. NAMING AND USP'S QUALITY STANDARDS FOR BIOLOGICS

USP has a well-evolved approach for setting standards for biologics and biotechnology-derived products that includes *USP* drug substance and drug product monographs as well as general chapters that support and complement these monographs. USP standards and associated Reference Standards define identity, strength, quality, and purity for both the biologic drug substance (active pharmaceutical ingredient) and the drug product. These standards also specify the established name for both the substance and product. They cover multiple manufacturers regardless of regulatory status; they evolve over time as science and regulations evolve, and they are part of globally harmonized approaches.

#### 1. Drug Names Provide a Critical Link to Public Quality Standards

As the monographs below demonstrate, USP standards apply at both the drug substance (Insulin Human) level and the drug product (Insulin Human Injection) level, with the nonproprietary name for the product grounded in the drug substance name. This link provides critical assurance to patients, providers, and other stakeholders that a drug is what it purports to be and meets the standards for strength, quality, and purity that are provided in the compendia.

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#### Insulin Human

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GVVHQQITSI CSLVQLFNYC N  
FVNHPLQVSH LVEALYLVCC ERGFETPKI

C<sub>257</sub>H<sub>383</sub>N<sub>65</sub>O<sub>77</sub>S<sub>6</sub> 5807.57  
Insulin (human) [11061-68-0].

##### DEFINITION

Insulin Human is a two-chain peptide hormone consisting of 51 amino acids, and its structure corresponds to native insulin produced *in vivo* by the beta cells of the pancreas. The A-chain is composed of 21 amino acids, and the B-chain is composed of 30 amino acids. It is either produced by methods based on recombinant DNA technology or derived by enzymatic modification of insulin from porcine pancreas to change the amino acid sequence appropriately. The presence of host cell DNA in Insulin Human is process-specific. The capability of the process to clear host-derived DNA requires validation and is determined by validated methods. Its potency is NLT 27.5 USP Insulin Human Units/mg, calculated on the dried basis.

[NOTE—One USP Insulin Human Unit is equivalent to 0.0347 mg of pure Insulin Human.]

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#### Insulin Human Injection

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##### DEFINITION

Insulin Human Injection is an isotonic, sterile solution of Insulin Human in Water for Injection. It has a potency of NLT 95.0% and NMT 105.0% of the potency stated on the label, expressed in USP Insulin Human Units/mL.

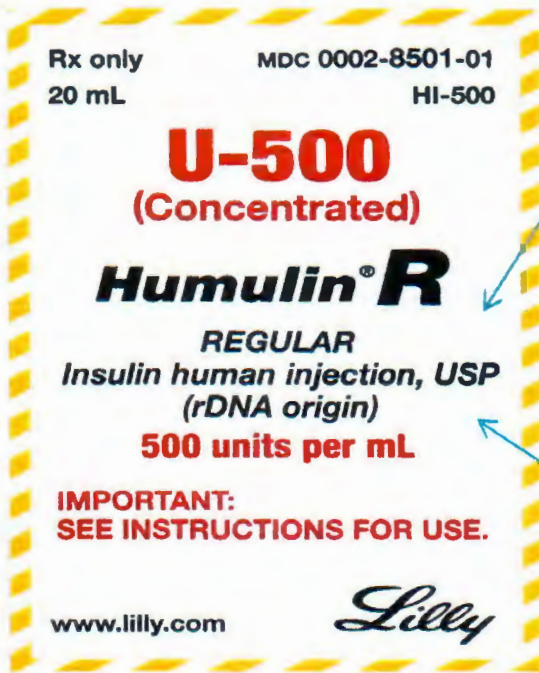
##### IDENTIFICATION

- **A.** The retention time of the major peak of *Sample solution A* or *Sample solution B* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

##### ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve and dispense in the unopened, multiple dose container provided by the manufacturer. Store in a refrigerator, protect from sunlight, and avoid freezing.
- **LABELING:** Label it to indicate that it has been prepared with Insulin Human produced by methods based on recombinant DNA technology or that it is derived by enzymatic modification of insulin from porcine pancreas. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units/mL.
- **USP REFERENCE STANDARDS (11)**  
USP Endotoxin RS  
USP Insulin Human RS

The label below demonstrates how the nonproprietary name specified in the monograph (Insulin Human Injection) links that product to USP's publicly available quality standard, which includes identification tests and appropriate acceptance criteria for purity, potency, and strength. This connection between the nonproprietary name on the label and the USP standard behind it provides traceability to publicly available quality tests and criteria that define the drug's identity and other critical quality attributes.



### **Insulin Human Injection**

#### **DEFINITION**

Insulin Human Injection is an isotonic, sterile solution of Insulin Human in Water for Injection. It has a potency of NLT 95.0% and NMT 105.0% of the potency stated on the label, expressed in USP Insulin Human Units/mL.

#### **IDENTIFICATION**

- **A.** The retention time of the major peak of *Sample solution A* or *Sample solution B* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

#### **ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve and dispense in the unopened, multiple-dose container provided by the manufacturer. Store in a refrigerator, protect from sunlight, and avoid freezing.
- **LABELING:** Label it to indicate that it has been prepared with Insulin Human produced by methods based on recombinant DNA technology or that it is derived by enzymatic modification of insulin from porcine pancreas. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units/mL.
- **USP REFERENCE STANDARDS (11)**  
USP Endotoxin RS  
USP Insulin Human RS

## **2. Non-Proprietary Naming in Evolving Multi-Manufacturing Environments**

For many decades, USP has been setting monograph standards for biologics and biotechnology-derived articles of all classes, from highly purified small peptides like insulin and glucagon to highly complex biological mixtures like pancreatin or heparin. Many of these monographs are for biologics from multiple manufacturers that have shared the same nonproprietary name, even as the product and associated regulatory expectations have evolved over time. The flexible monograph<sup>4</sup> mechanism allows for accommodation of multi-source materials as well as application of different, yet equivalent, procedural approaches to the determination of established quality attributes for a given molecule.

It is important to note that the fact that products share the same compendial name does not mean that they are comparable or interchangeable and does not confer regulatory status. Only the relevant regulator has the authority under various laws to clear a drug for marketing or to determine that two or more drugs are the same, similar, or interchangeable. USP monograph tests establishing identity may cover multiple articles in commerce that

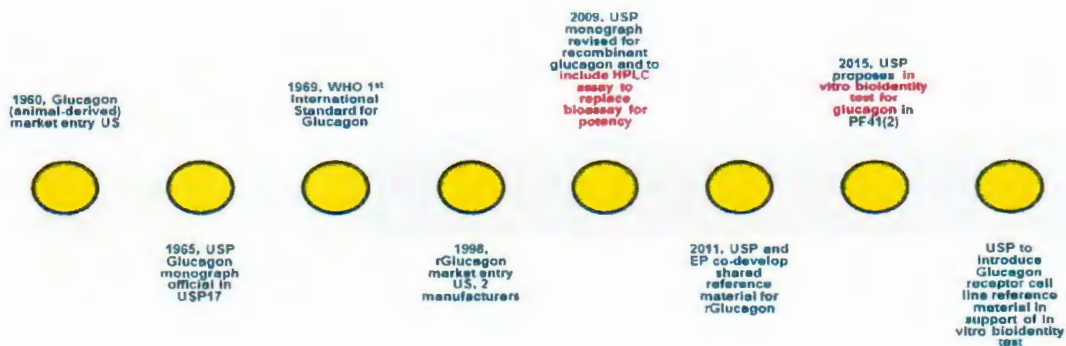
<sup>4</sup> The USP 'flexible monograph' allows different tests, procedures, and/or acceptance criteria, depending on characteristics that do not affect the primary safety and efficacy of a drug; e.g., different Impurity tests to account for different impurities arising from different routes of production.



share the same nonproprietary name but have not been found to be similar or interchangeable by FDA.

Examples include Glucagon, a long-established diabetes medicine that has been on the U.S. market since 1960. As illustrated below, it was originally a naturally derived product, but currently it is a recombinant biotechnology product made by multiple manufacturers, licensed as non-interchangeable (Figure 3). Most recently, in May 2015, through the advances of organic chemistry, it has also been licensed in the United States as a completely synthetic peptide, also licensed as non-interchangeable. Along with these developments, both national and international standards have evolved to allow the maintenance of appropriate and common quality expectations for products under the same name with shared key quality attributes, most importantly substance identity.

Figure 3.



Throughout these developments, the products have continued to share the same nonproprietary names, which are the official titles specified in the USP monographs: for the Glucagon drug substance the official title is *Glucagon*, and for the drug product the official title is *Glucagon for Injection*. These nonproprietary names/official titles are scientifically based—the shared nonproprietary name for the drug substances reflects the fact that they are the same chemical entity (in the case of Glucagon, share the same unmodified primary protein sequence). They also share other key common attributes that define quality, strength, and purity. This is important, because in a typical USP drug substance monograph several tests directly probe the substance identity and establish what the drug is and whether the standard applies.

Another example of a multi-manufacturer biologic is Somatropin, human growth hormone. USP has both an official drug substance monograph (*Somatropin*) and a drug product monograph (*Somatropin for Injection*). As with Glucagon, these monographs contain key quality attributes that link directly to the nonproprietary name. For example, the current modern USP drug substance monograph contains three separate and orthogonal tests for identity, and at least one of them directly probes the primary structure, as shown below (Figure 4).

Figure 4.

**Somatropin Drug Substance Monograph - Identity**

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**Somatropin**

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$C_{222}H_{1528}N_{262}O_{310}S_7$  22,124-77 [12629-01-5]

**Identity Tests:**

1. Chromatographic Purity by HPLC
2. Peptide Mapping

**Bioidentity. Bioassay**

Several orthogonal procedures should probe different identifying attributes of the article, including the primary sequence.

The excerpt from the USP-USAN Dictionary shown below illustrates how Somatropin drug substances from different manufacturers in the US market that share this common identity share the same nonproprietary name as well as the same UNII or substance registration code, as maintained by FDA and USP (Figure 5).

Figure 5.

### Somatropin Example

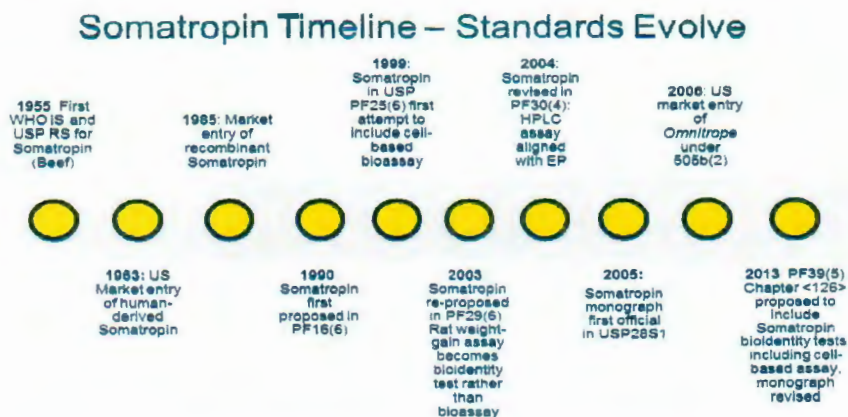
Somatropin - (soe' ma troe' pin)

Date	1977
Official Compensible	USP
Molecular Info	$C_{222}H_{1528}N_{262}O_{310}S_7$ 22,124-77
Proprietary Name	INN: BAN, IAN
Chemical Name	Polypeptide growth hormone (hGH) (A single polypeptide chain of 191 amino acids having the primary structure of the polypeptide chain obtained by hydrolysis of growth from the anterior lobe of the human pituitary gland - 1) (USP Reference Standard) (BAN) (2) Somatropin (INN)
UNII codes	ORII AQJ9K6R4Z
CAS Number	CAS-12629-01-5
Category	Human (growth)
Manufacturer Info	Lyphochrom, Inc. Multiple (10), Reference (multiple), Soluble (multiple), Somatropin (multiple)
Code Descriptions	QAS 411 171 QAN6

FVTPVSRF	DNAMBAHR	HQLAFDTIQE	FFFAVPRKEQ	KFFFLQWPQT
NLEFSEVFF	PIARF IQDK	SNLELRISL	LLIQSWEPV	QLRSWFANS
LVIQASDQW	YDLRKEFEG	IQILMGRLEH	QSPRTGQIFK	QIYKRFDTNS
HNDALLKTY	VALYGRADM	TRVETFLREY	QCRSVEGSDG	I

Like Glucagon, Somatropin is a biological medicine that has evolved over time. As with Glucagon, USP's current modern standards for Somatropin have evolved with the science and in international dialog, as the timeline below illustrates (Figure 6).

Figure 6.



The third, most recent relevant example is Filgrastim, human granulocyte-stimulating factor, used in the chemotherapy recovery of cancer patients. USP's drug substance monograph follows the same approaches established above for Somatropin and Glucagon. The modern monograph covers key quality attributes of the Filgrastim molecule relevant to both the innovator molecule and the recently licensed biosimilar Filgrastim-sndz.<sup>5</sup> In the Filgrastim monograph, as shown below, identity is covered by three tests, one of which is peptide mapping that links directly to the primary amino acid sequence of the substance.

### Filgrastim

$C_{645}H_{1111}N_{42}O_{447}S_2$  18,799 daltons  
[121181-53-1]

**DEFINITION**

Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains NLT 0.9 mg/mL of Filgrastim. Formulation contains one or more suitable buffering and/or stabilizing agents. The presence of host cell DNA and protein in Filgrastim is process-specific. The capability of the process to clear host-derived DNA and protein requires validation and is determined by validated methods. It has a biological potency of NLT 80% and NMT 125% relative to standard on a mass-to-mass basis.

**IDENTIFICATION**

- **A.** It meets the requirements in the Assay.
- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained as directed in the test for Organic Impurities, Related Compounds.
- **C. PEPTIDE MAPPING**  
(See *Biotechnology-Derived Articles—Peptide Mapping* (1055).)

<sup>5</sup> See, [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2015/125553Orig1s000ChemR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125553Orig1s000ChemR.pdf).

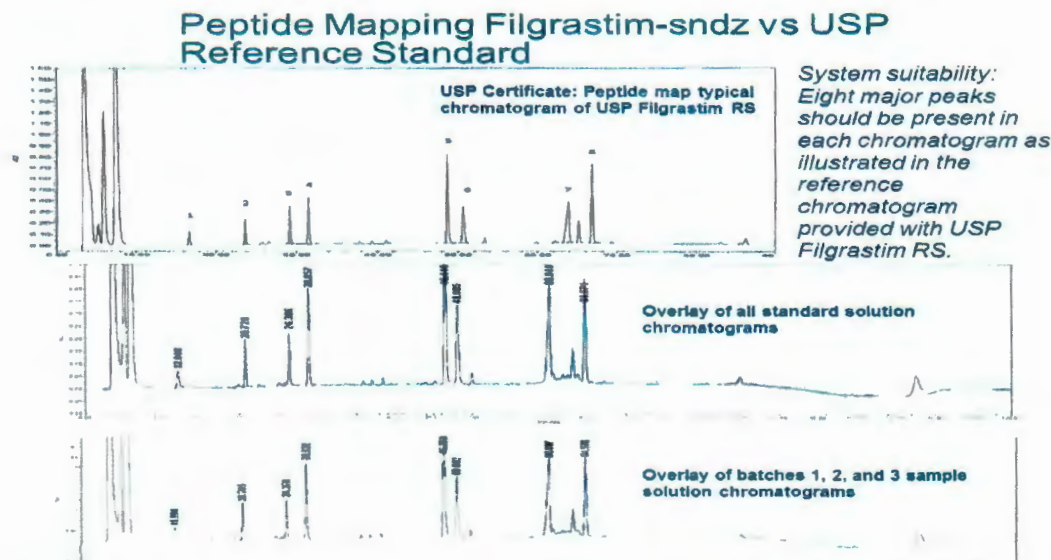
It is important to note that all currently US-licensed Filgrastim products (including tbo-Filgrastim, brand name *Granix*) again share the same UNII code for substance, as shown below (Figure 7).

Figure 7.

Filgrastim - (fil grae stim).	
Date	[1990]
Official Compendia	USP.
Molecular Info	C <sub>845</sub> H <sub>1339</sub> N <sub>223</sub> O <sub>243</sub> S <sub>9</sub> . 18,800 daltons.
Nonproprietary Name	INN; BAN.
Chemical Name	A single chain, 175 amino acid polypeptide, nonglycosylated, expressed by <i>E. coli</i> . (1) Colony-stimulating factor (human clone 1034), <i>N</i> -L-methionyl-; (2) <i>N</i> -L-homothionylcolony-stimulating factor (human clone 1034).
UNII Codes	UNII-PV15MOM1GW.
CAS Numbers	CAS-121181-53-1.
Category	Antineutropenic; hematopoietic stimulant.
Manufacturer Info	Neupogen (Amgen)
Code Designations	◇r-methuG-CSF
MTPLGPASSL PQSFLKCLE QVRKIQDGA ALQEKLCATY KLCHPEELVL LGHSLGIPWA PLSSCPSQAL QLAGLSQLH SGLFLYQGLL QALEGISPEL GPTLDTLQLD VADFATTIWQ QMEELGMAPA LQPTQGAMPA FASAFQRRAG GVLVASHLQS FLEVSRYVLR HLAQP	
Tbo-filgrastim - (tee boe - fil grae stim).	
UNII Codes	UNII-PV15MOM1GW.
CAS Numbers	CAS-121181-53-1.

USP laboratories have recently analyzed three drug substance lots of the Filgrastim-sndz biosimilar and confirmed that the material conforms with all requirements of the USP *Filgrastim* drug substance monograph (see Figure 8, detailed findings will be presented in USP's comments to FDA's Proposed Rule). Under the time-tested approach used for Glucagon, Somatropin, and many other products, because the Filgrastim-sndz drug substance meets the identity specified in the monograph, the official title *Filgrastim* would apply as the nonproprietary name.

Figure 8.



Maintaining linkage of the same nonproprietary name to products with the same key quality attributes, especially with regard to molecule identity and potency, has been and continues to be an important component of advancing the global scientific quality understanding and the public health impact of these products. The table below describes international agreement on key standards for these and other products under the same name for key attributes such as potency (Figure 9).

Figure 9.

Substance	Potency	Compendia	International Standard	Source	Harmonized Tests?	Labeling
Insulin Human	28.82 IU/mg 28.82 USP U/mg	USP and EP, USP unit =IU	yes	Recombinant	Mostly, EP: no bioassay	Units
Somatropin	3 IU/mg 3 USP U/mg	USP and EP USP unit = IU	Yes	Recombinant, mass assigned	Mostly, EP: no bioassay	mg
Glucagon	1 IU/mg NLT 0.8 USP U/mg	USP and EP USP and IU are assumed equivalent	Yes	Porcine	Mostly, EP: no bioassay	mg and U, assuming 1U/mg
Filgrastim	NLT 0.9 x10 <sup>9</sup> IU/mg of protein	USP and EP, IU in both	Yes	Recombinant	Mostly	mg

This table also reflects the important links between these common names and compendial and internationally recognized reference materials. Biological activity plays a key role in the establishment of molecule identity, the so-called bioidentity, and establishment of reliable bioassay data is heavily reliant on the availability of appropriate reference materials. Establishment of appropriate measurement chains for these standards relies on scientifically based naming for related and identical substances.

#### IV. IMPLICATIONS OF FDA'S PROPOSED APPROACH

The Draft Guidance proposes that all newly licensed and previously licensed biological products be given a "proper name" consisting of a core name and a unique FDA-designated suffix attached with a hyphen. According to the Draft Guidance, such a naming convention would help prevent inadvertent substitution and promote safe use by signifying that related biological products may not have been licensed for the same route of administration or packaged with the same delivery system, and that such products have not been determined to be interchangeable. Additionally, the Draft Guidance indicates that FDA believes such a convention would facilitate pharmacovigilance for biological products.

USP appreciates the challenge of ensuring safe use and facilitating pharmacovigilance in the implementation of the new licensure pathway for biosimilar and interchangeable biological products under BPCIA. However, USP is concerned that in attempting to address some of these challenges through the nonproprietary naming system, which was never designed or intended to serve such purposes, the proposal in the Draft Guidance could create unintended consequences.

The nonproprietary naming system was intended to establish simple and scientifically useful names and has never been intended to convey regulatory status. Establishing nonproprietary names based on shifting regulatory expectations, as proposed by FDA in the Draft Guidance, could dilute well-established scientific principles and understanding of drug and biologic substances and products. This would also be a departure from establishing such names based on well-established scientific principles for chemical and biological entities with defined properties. This has implications globally as well as in the US, as many established drugs and biologics are linked to existing internationally harmonized efforts that are increasingly important in a global pharmaceutical marketplace.

Additionally, the proposal in the Draft Guidance could have the unintended effect of creating confusion, potentially placing patients in harm's way through medication errors and disruption of pharmacy systems. Some commentators have expressed the possibility that prescribers and dispensers may not be able to recall non-distinctive suffixes.

Manufacturing and pharmacy organizations have also expressed a concern that different nonproprietary names could affect data transfer within the US and abroad and that even small, seemingly inconsequential changes in product descriptions could have the potential to create significant consequences within healthcare systems.

The proposal could also create obstacles to global trade and harmonization, creating requirements that are viewed by other countries as an unfair restraint of trade, balkanizing national approaches, and making it more difficult to create globally interoperable systems.

It is not possible to predict to what extent these issues might occur. However, given the uncertainty and potential risks created by deviating from the existing long-standing and well-recognized naming system, USP urges FDA to consider whether its goals might be achieved through other mechanisms.

## **V. POTENTIAL SOLUTIONS**

As discussed above, USP has a recognized role in the misbranding and adulteration provisions of the FDCA. USP's labeling requirements are also separately recognized in FDCA 502(g). These statutory provisions clearly distinguish between compendial naming on the one hand, and compendial labeling requirements. FDA regulations also reflect the distinction between the role of the nonproprietary name (official title) on the label and other labeling requirements that include information and text in addition to the established name of the drug or ingredients.<sup>6</sup>

USP believes that labeling is potentially one avenue for addressing the concerns that prompted the approach in the Draft Guidance, without the unintended consequences noted above. Specifically, we would propose the inclusion of a suffix in USP labeling requirements, without designating it as part of the nonproprietary name, to ensure that the qualifier remains closely linked to the name and can be used to identify and trace products back to their manufacturers.

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<sup>6</sup> 21 CFR § 201.10(a), (g)(1)-(2)), & (i), (Drugs; statement of ingredients); 21 CFR § 201.50 (Statement of Identity) (2015).

In addition to providing a resolution achievable under the FDCA, USP believes that such a solution would facilitate a common global approach to the naming of biological products that would be built on and consistent with existing, accepted scientific principles. USP continues to support the efforts of the WHO's INN expert group in the context of international nonproprietary naming, specifically the recent WHO INN Biological Qualifier (BQ) proposal.<sup>7</sup> Under the BQ proposal, unlike the proposal in the Draft Guidance, the BQ suffix would not be made part of the INN, thus maintaining existing naming systems.

Again, we appreciate FDA's efforts to address the challenges of implementing the biosimilars pathway, including naming, and remain committed to working collaboratively with the Agency to advance our common goal of protecting and promoting the public health.

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<sup>7</sup> See, [http://www.who.int/medicines/services/inn/bq\\_innproposal201506.pdf.pdf?ua=1](http://www.who.int/medicines/services/inn/bq_innproposal201506.pdf.pdf?ua=1).